Remarks

Applicants appreciate the Examiner's acknowledgment that claims 1-15, 22-24, and 69-71 are allowable over the prior art of record.

The Amendments

The following amendments suggested in the final Office Action have been made:

- claims 9, 10, 14, 15, 24, and 69 have been amended to recite "the coding sequence" in place of "a coding sequence";
- claims 74 and 75 have been amended to delete all recitations of "(a)" and "(b)" as redundant with respect to the "first" and "second" polynucleotides; and
- claims 74-77, 79-81, and 83 have been amended to recite "% identical in sequence."

Independent claims 74 and 75 have been amended to recite that the second polynucleotide "is at least 96% identical" and "at least 300 nucleotides." The recitation of "96% identical" is supported by now canceled claims 78 and 82. The recitation of "at least 300 nucleotides" is supported at page 10, lines 9-12: "[t]ransmembrane serine protease polypeptides according to the invention comprise at least 10, 15, 25, 50, 75, 100 125, 150, . . . contiguous amino acids selected from SEQ ID NO: 12 or a biologically active variant thereof." Because each amino acid is encoded by a three-nucleotide codon, a polypeptide comprising at least 100 contiguous amino acids is encoded by a polynucleotide comprising at least 300 contiguous nucleotides. Similar amendments have been made to dependent claims 76, 77, 79-81, and 83.

New claims 84 and 85 are directed to polynucleotide probes. The probes have recited characteristics similar to the second polynucleotides recited in amended claims 74 and 75, respectively. Claims 84 and 85 differ from claims 74 and 75 in that they recite that the

polynucleotide "comprises at least 450 nucleotides." This recitation is supported at page 24, lines 5-8 and page 10, lines 9-12, quoted above. Claims 76, 77, 80, and 81 have been amended to recite dependency on new claims 84 and 85 in place of claims 74 and 75.

None of the amendments introduces new matter or requires a new search. The amendments were not made earlier because Applicants believed that the amendments and arguments filed June 10, 2003 in response to the last Office Action were sufficient to overcome the rejections of the claims. Applicants have also not added any new claims without canceling at least an equal number of currently pending claims. We believe that these amendments place the claims in condition for allowance.

Claim Objections

Claims 9, 10, 14, 15, 24, and 69 are objected to as being informal for reciting "a coding sequence." As suggested in the final Office Action, the claims have been amended to recite "the coding sequence."

Applicants respectfully request withdrawal of the objection.

The Rejection of Claims 74-83 Under 35 U.S.C. § 112, second paragraph

Claims 74-83 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 78 and 82 have been canceled. Applicants respectfully traverse the rejection of claims 74-77, 79-81, and 83.

First, the final Office Action asserts that the recitation of first and second polynucleotides together with "(a)" and "(b)" renders independent claims 74 and 75 indefinite. The recitations of "(a)" and "(b)" have been deleted from claims 74 and 75.

Second, the final Office Action asserts that the recitations of "% identical" in claims 74-83 is unclear because the basis for comparison is not set forth. As suggested in the final Office Action, claims 74-77, 79-81, and 83 have been amended to recite "% identical in sequence."

Third, the final Office Action asserts that the recitations "polynucleotide that hybridizes under stringent conditions along the full length of at least 225 contiguous nucleotide of the nucleotide sequence shown in SEQ ID NO:11, wherein the second polynucleotide is at least 70% identical to the at least 225 contiguous nucleotides of the first polynucleotide" (independent claim 74) and "polynucleotide that hybridizes under stringent conditions along the full length of at least 225 contiguous nucleotides of the nucleotide sequence of the cDNA insert of plasmid pCRII-TMSP3, wherein the second polynucleotide is at least 70% identical to the at least 225 contiguous nucleotides of the first polynucleotide" (independent claim 75) render claims 74 and 75 indefinite. The final Office Action asserts that these recitations are unclear because it is uncertain how to determine whether a polynucleotide that is not perfectly matched to a reference sequence hybridizes along the full length of the reference sequence. Paper 15, page 4, lines 8-11. The final Office Action also asserts that these recitations are unclear because the polynucleotide to which the polynucleotide probes are at least 70% identical is not specified. Paper 15, page 4, lines 11-14. Claim 74 has been amended to recite that "the second polynucleotide is at least 96% identical in sequence to the complete complement of SEQ ID NO:11, wherein the second polynucleotide comprises at least 300 nucleotides." Claim 75 has been amended to recite that

"the second polynucleotide is at least 96% identical in sequence to the complete complement of the cDNA insert of plasmid pCRII-TMSP3, wherein the second polynucleotide is at least 96% identical in sequence to the complete complement of the nucleotide sequence of the cDNA insert of plasmid pCRII-TMSP3." The amendments remove the recitation that the polynucleotide probes "hybridize along the full length" of a reference polynucleotide. The amended claims explicitly recite the sequence with which the polynucleotide probes share the recited percent sequence identity.

Applicants respectfully request withdrawal of this rejection.

The Rejection of Claims 74-83 Under 35 U.S.C. § 112, First Paragraph

Claims 74-83 stand rejected under 35 U.S.C. § 112, first paragraph as containing new matter, lacking enablement, and lacking written description. Each of these bases for rejection is discussed separately below.

New Matter

The final Office Action asserts that claims 74-83 contain new matter. Claims 78 and 82 have been canceled. Applicants respectfully traverse the rejection of claims 74-77, 79-81, and 83.

The final Office Action asserts that the specification lacks "adequate support for a polynucleotide which hybridizes under the conditions recited and has at least 70%, 75%, 90%, 96% or 98% sequence identity to any fragment of the complete complement of the polynucleotide of SEQ ID NO:11 or the cDNA insert of plasmid pCRII-TMSP3." Paper 15, page 5, lines 21-24, emphasis in original.

First, the amended claims no longer recite "the complete complement." Second, contrary to the assertion in the final Office Action, the specification discloses that hybridization conditions, *e.g.*, a particular calculated melting temperature used during hybridization, are linked to the percent sequence identity of the polynucleotide probe to a serine protease coding sequence: "It is well known that the T_m of a double-stranded DNA decreases by 1-1.5°C with every 1% decrease in homology." Page 14, lines 11-15. Thus a hybrid between a polynucleotide probe and a serine protease coding sequence will have a melting temperature that depends on the percent sequence identity between the probe and the serine protease coding sequence. The specification teaches how to calculate the melting temperature for a hybrid between a serine protease coding sequence and a polynucleotide probe based on sequence identity:

> Typically, for stringent hybridization conditions a combination of temperature and salt concentration should be chosen that is approximately 12-20°C below the calculated T_m of the hybrid under study. The T_m of a hybrid between a transmembrane serine protease polynucleotide having a coding sequence disclosed herein and a polynucleotide sequence which is at least about 50, 55,5 60, 65, 70, preferably about 75, 90, 96, or 98% identical to that nucleotide sequence can be calculated, for example, using the equation of Bolton and McCarthy:
>
> $T_m = 81.5°C-16.6(\log_{10}[Na^+]) + 0.41(\%G + C) - 0.63(\%formamide) - 600/l$,
>
> where l = the length of the hybrid in basepairs.

Page 14, line 22 to page 15, line 2, citation omitted. Thus, independent claims 74 and 75 do not contain new matter.

Applicants respectfully request withdrawal of this rejection.

Written Description

Claims 74-83 are rejected as lacking adequate written description. Claims 78 and 82 have been canceled. Applicants respectfully traverse the rejection of claims 74-77, 79-81, and 83.

To comply with the written description requirement, the description must clearly convey to persons of ordinary skill in the art that applicants invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). The specification meets this requirement.

The final Office Action asserts that claims 74-77, 79-81, and 83 are drawn to "a genus of polynucleotides of any function" and that the specification does not adequately describe this large genus. Paper 15, paragraph bridging pages 6-7. Claims 74 and 75 are the independent claims of the rejected claim set. Each of these claims is directed to polynucleotide probes selected from a group consisting of a first and a second polynucleotide. The genera of first and second polynucleotides are not as large as asserted in the final Office Action.

Claim 74 has been amended to recite that the first polynucleotide consists of at least 300 contiguous nucleotides of the complete complement of SEQ ID NO:11. Claim 75 has been amended to recite that the first polynucleotide consists of at least 300 contiguous nucleotides of the complete complement of the nucleotide sequence of the cDNA insert of plasmid pCRII-TMSP3. Thus, the first polynucleotide of each independent claim contains only nucleotide sequences present in the complement either of SEQ ID NO:11 or of the cDNA insert of plasmid pCRII-TMSP3. The specification discloses the nucleotide sequence of SEQ ID NO:11. The plasmid pCRII-TMSP3 has been deposited. See the specification at page 88, line 23 to page 89, line 2:

> The PCR products were cloned into the pCRII vector (Invitrogen) and sequenced. The nucleotide and amino acid sequences are shown in SEQ ID NOS:11 and 12, respectively. . . .
>
> A plasmid containing a cDNA encoding the pCRII-TMSP3, was deposited under the provisions of the Budapest Treaty with the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209 on June 5, 2001, and assigned Accession No. 3433.

One of skill in the art, having the knowledge of the rules of complementary base pairing, would have understood that applicants had possession of the complement of the disclosed coding sequence either of SEQ ID NO:11 or of the cDNA insert of pCRII-TMSP3 when this application was filed. The specification also discloses polynucleotides that consist of at least 300 nucleotides of these coding sequences. The specification teaches that transmembrane serine protease polypeptides comprise at least 100 contiguous amino acids selected from SEQ ID NO:12 (page 10, lines 9-11) and probes that hybridize to polynucleotides encoding a transmembrane serine protease polypeptide (page 24, lines 5-8). Thus the disclosed probes include polynucleotides encoding at least 100 contiguous amino acids of SEQ ID NO:12, *i.e.*, at least 300 nucleotides. The specification adequately describes the genus of first polynucleotides recited in claims 74 and 75.

The second polynucleotide of claim 74 hybridizes under specifically recited conditions to the nucleotide sequence shown in SEQ ID NO:11, is at least 96% identical in sequence to the complete complement of SEQ ID NO:11, and comprises at least 300 nucleotides. The second polynucleotide of claim 75 hybridizes under specifically recited conditions to the nucleotide sequence of the cDNA insert of plasmid pCRII-TMSP3, is at least 96% identical in sequence to the complete complement of the nucleotide sequence of the cDNA insert of plasmid pCRII-TMSP3, and comprises at least 300 nucleotides. Thus, the at least 300 nucleotide second

polynucleotide must be at least 96% identical in sequence to the complement of SEQ ID NO:11 or the cDNA insert of plasmid pCRII-TMSP3. A polynucleotide having these characteristics must share at least 288 identical nucleotides with the complement of SEQ ID NO:11, *i.e.*, 300 nucleotides x .96.

As discussed above, one of skill in the art would have recognized that applicants had possession of the genera of polynucleotides that are the complement of SEQ ID NO:11 or the complement of the cDNA insert of plasmid pCRII-TMSP3. The specification teaches polynucleotide probes that are at least 96% identical in sequence to the complements of SEQ ID NO:11 and the cDNA insert of plasmid pCRII-TMSP3 and that hybridize to the recited target polynucleotides under the recited conditions. Furthermore, the specification discloses that these sequences can comprise 300 nucleotides. The specification adequately thus describes the subject matter of claims 74-77, 79-81, and 83. Applicants respectfully request withdrawal of this rejection.

Enablement

The final Office Action asserts that claims 74-83 are not enabled. Claims 78 and 82 have been canceled. Applicants respectfully traverse the rejection of claims 74-77, 79-81, and 83.

The final Office Action asserts that "the specification, while enabling for a polynucleotide consisting of 225 contiguous nucleotides of the polynucleotide of SEQ ID NO:11, does not reasonably provide enablement for polynucleotides of any function wherein said polynucleotides hybridize to the polynucleotide of SEQ ID NO:11 or the cDNA insert of pCRII-TMSP3 under stringent conditions." Paper 15, page 8, lines 5-9, emphasis in original.

The polynucleotides that hybridize under stringent conditions are the second polynucleotides recited in each of independent claims 74 and 75. First, as discussed in the response to the written description rejection, this genera of polynucleotides is not as broad as asserted in the Office Action. The second polynucleotide recited in claim 74 is at least 96% identical to the complement of SEQ ID NO:11, hybridizes at a recited melting temperature, and comprises at least 300 nucleotides. The second polynucleotide recited in claim 75 is at least 96% identical to the complement of the cDNA insert of plasmid pCRII-TMSP3, hybridizes at a recited melting temperature, and comprises at least 300 nucleotides.

Second, the scope of the recited second polynucleotides in claims 74 and 75 must bear a reasonable correlation to the scope of enablement provided in the specification. *In re Fisher*, 427 F.3d 833, 839 (C.C.P.A. 1970). Only one disclosed use need by enabled. *Engel Industries, Inc. v. Lockformer Company*, 946 F.2d 1528, 1533 (Fed. Cir. 1991). The specification enables the use of the full scope of the recited polynucleotides as probes to detect a transmembrane serine protease polynucleotide. The specification teaches that "[t]he presence of a polynucleotide sequence encoding a transmembrane serine protease polypeptide can be detected by DNA-DNA or DNA-RNA hybridization or amplification using probes or fragments of polynucleotides encoding a transmembrane serine protease polypeptide." Page 24, lines 5-8. Methods of using probes to detect polynucleotides, *e.g.*, Northern Blotting, Southern Blotting, *in situ* hybridization, were well known in the art at the time the application was filed and their performance by those skilled in the art was routine.

The final Office Action also faults the specification because it "does not disclose the critical structural element required in a polynucleotide to display serine protease activity, nor

does it disclose which 225 nucleotides are essential for serine protease activity." Paper 15, page 7, lines 14-16. Such disclosure is not required to enable the claimed probes. First, polynucleotides do not have serine protease activity. Second, the claimed polynucleotide probes are *complementary* to coding sequences for serine proteases and do not encode any protein.

Applicants respectfully request withdrawal of this rejection.

The Rejection of Claims 74-83 Under 35 U.S.C. § 102(b)

Claims 74-83 stand rejected under 35 U.S.C. §102 (b) as being anticipated by Dias Neto *et al.*, GenBank accession number AW845106 ("Dias Neto"). Claims 78 and 82 have been canceled. Applicants respectfully traverse the rejection of claims 74-77, 79-81, and 83.

To reject a claim as anticipated each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). See also M.P.E.P. § 2131. Dias Neto does not meet this standard.

Claims 74 and 75 are the independent claims of the rejected claim set. Each of these claims is directed to polynucleotide probes selected from a group consisting of a first and a second polynucleotide. Dias Neto is cited as teaching a polynucleotide that comprises 285 consecutive nucleotides of the polynucleotide of SEQ ID NO:11. Paper 15, page 11, lines 7-9. Independent claim 74, as amended, recites a polynucleotide consisting of at least 300 contiguous nucleotides of the complete complement of SEQ ID NO:11. Dias Neto does not teach a polynucleotide consisting of at least 300 contiguous nucleotides of SEQ ID NO:11. Thus Dias Neto does not teach the first polynucleotide recited in amended claim 74.

The second polynucleotide of claim 74 "is at least 96% identical in sequence to the complete complement of SEQ ID NO:11, wherein the second polynucleotide comprises at least 300 nucleotides." A polynucleotide having these characteristics must share at least 288 identical nucleotides, *i.e.*, 300 nucleotides x .96, with the complement of SEQ ID NO:11. As indicated above, Dias Neto teaches a nucleotide sequence of which only 285 nucleotides are identical to nucleotides of SEQ ID NO:11. Thus, Dias Neto also does not teach the second polynucleotide recited in claim 74.

Claim 75 is identical to claim 74 except that the nucleotide sequence recited in claim 75 is "the cDNA insert of pCRII-TMSP3" and not "SEQ ID NO:11." SEQ ID NO:11 represents the coding sequence of the cDNA insert of pCRII-TMSP3. See page 88, line 23 to page 89, line 2 of the specification, quoted above. Thus, Dias Neto also does not teach the first or the second polynucleotide recited in claim 75.

Dias Neto does not teach each and every element recited in independent claims 74 and 75 or dependent claims 76, 77, 79-81, and 83. Dias Neto thus does not anticipate these claims. Applicants respectfully request withdrawal of this rejection.

Respectfully submitted,

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By: Lisa M. Hemmendinger
Lisa M. Hemmendinger
Registration No. 42,653

Banner & Witcoff, Ltd.
1001 G Street, N.W., Eleventh Floor
Washington, D.C. 20001-4597
(202) 824-3000